REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 21-23, 33-35, and 45-47 are pending and under active consideration in this application.

2. Patentability Remarks

a. 35 U.S.C. §§ 101 and 112, first paragraph

On pages 2-13 of the Office Action, the Examiner rejects claims 21-23, 33-35, and 45-47 under 35 U.S.C. § 101 for allegedly lacking a specific and substantial utility, and a well-established utility. The Examiner also rejects these claims under 35 U.S.C. § 112, first paragraph for allegedly lacking utility. In order to satisfy the utility requirement, a specific and substantial utility must either (i) be cited in the specification or (ii) be recognized as well as established in the art, and the utility must be credible. *See In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005) and *Revised Interim Utility Guideline Training Materials* ("Guidelines").

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See Fisher*, 421 F.3d at 1371 and *Guidelines*. Applicant respectfully submits that the application provides a specific utility for the nucleic acids related to the GAM2191 hairpin having SEQ ID NO: 2194 in accordance with *Fisher* and *Guidelines*.

Specifically, the nucleic acid having SEQ ID NO: 2194, which Applicant elected in the office action reply submitted on September 21, 2006, produces two miRNAs–one each from its 5' and 3' arms. Claims 22, 34, and 46 are related to the 5' miRNA with SEQ ID NO: 5264 (the "5'MIR"). The 3' miRNA is depicted in Table 2, lines 151,383-151,482 of the application as filed. This "3'MIR" is also shown below.

GENE	TARGET	UTR	SEQUENCE	SEQID	BINDING-SITE
GAM2191	MAP1B	3'	ACTAAAGAATGCCTACTGC	25389	ACTAGGGAA __ CC C ||||||||| || ||||| TGATTTCTT GG TGACG AC A

In order to establish the utility of the claimed nucleic acids related to the elected hairpin, Applicant presents data below demonstrating that the 3'MIR regulates expression of the target gene MAP1B (SEQ ID NO: 25389).

Applicant submits that the nucleic acids related to GAM2191 hairpin such as the 3'MIR have specific utility. In *Fisher*, the claims at issue were directed to five (5) out of more than 32,000 EST that were disclosed in the application. Each of disclosed ESTs were from a cDNA library of pooled leaf tissue isolated from a maize plant. The *Fisher* application did not disclose the location of the ESTs in the genome or the function of the underlying genes. *Fisher* asserted that the utilities for claimed ESTs were (1) serving as a molecular marker; (2) measuring the level of mRNA in a tissue sample; (3) providing a source of primers for PCR of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *See Fisher*, 421 F.3d at 1367-1368. It is important to note that each of the utilities asserted were not limited to any specific gene, genetic location or protein.

The *Fisher* court concluded that the asserted utilities were clearly not "specific." The court explained that any EST transcribed from any gene in maize could perform the seven uses such as being a molecular marker, a primer, or measure the level of RNA in a tissue sample. In other words, nothing about the seven alleged uses separated the claimed ESTs from the vast number of other ESTs also disclosed in the application. The keystone to the lack of specific utility in *Fisher* is that the claimed ESTs **did not correlate to an underlying gene of known function found in the maize genome**.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids may be used to target and modulate expression of **specific** gene transcripts. Specifically, Table 2, lines 151,383-151,482 as shown above, discloses that the 3'MIR specifically targets mRNA transcripts of the target gene MAP1B. Consequently, the claimed nucleic acids are of a **specific and unique nature** because these nucleic acids regulate the translation of mRNAs from the **specific target gene MAP1B**. Accordingly, the asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating MAP1B.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, it must be shown that the asserted use of the claimed invention has a significant and presently available benefit to the public. *See Id. at* 1371 and *Guidelines*. Applicant respectfully submits that the application provides a substantial utility for the nucleic acids related to the hairpin GAM2191 in accordance with *Fisher* and *Guidelines*.

In *Fisher*, it was admitted that the underlying genes for the ESTs had no known function. *Fisher* argued that this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, *Fisher* failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Fisher*, 421 F.3d at 1373, *quoting Brenner v. Manson*, 383 U.S. 519 (1966).

In contrast to *Fisher*, the present application discloses that the 3'MIR may be used to bind and regulate mRNA transcripts of MAP1B. *Instant Application,* Table 2, lines 151,383-151,482. In addition, MAP1B is known to be a microtubule-associated protein. *See* DiTella, *et al.*, Jo Cell Sci, 1996;109:467-77. MAP1B protein promotes tubulin assembly and microtubule stability during active process extension. *Id.* The protein is expressed in cerebellar macroneurons when these cells are plated, and during the initial phases of neurite outgrowth and axonal elongation. *Id.* Compared to plating on polylysine, plating these cells on laminin leads to rapid incorporation of MAP1B into the cell protein fraction associated with axonal outgrowth. *Id.* Suppressing expression of MAP1B in laminin-plated neurons significantly reduces the rate and extent of axonal elongation induced by laminin. *Id.* Because MAP1B incorporation plays a critical role in laminin-induced axonal elongation, MAP1B expression could be modulated *in vitro* to alter active axon extension in neurons

The evidence described above clearly supports that the 3'MIR has a number of presently available benefits to the public. Such benefits are the ability to modulate the expression of MAP1B in order to alter active axon extension in neurons. In view of the application providing particular targets of known function for the 3'MIR, Applicant respectfully submits that the specific and substantial utility requirements are satisfied in accordance of *Fisher* and *Guidelines*.

(3) Credible Utility

On page 8 of the Office Action, the Examiner asserts that there would have been reason to doubt the objective truth of the asserted utility of the claimed subject matter because there is no experimental evidence of even a single biological function for instant SEQ ID NO: 2194. Applicant submits herewith the declaration of Dr. Ayelet Chajut, Ph.D. under 37 C.F.R. § 1.132 (the "Chajut Declaration"), which presents experimental evidence that the 3'MIR is naturally expressed and regulates the asserted target MAP1B. The results described in the Chajut Declaration are summarized below.

Dr. Chajut conducted experiments that confirmed that the 3'MIR is expressed in HIV-infected c.Magi cells. *See Id.* at item 7. Microarray experiments show that the level of the 3'MIR is higher in HIV-infected cells compared to the background levels demonstrated in uninfected cells. Applicant submits that the experiments described in the Chajut Declaration establish that the 3'MIR is expressed by HIV and regulate the asserted target MAP1B.

Dr. Chajut also supervised and conducted experiments yielding results that are consistent with an ability of the 3'MIR to bind to and regulate the target MAP1B. *See the Chajut Declaration*, at items 4-7. Specifically, the experiments entailed infecting c.Magi cells with HIV, which expresses the 3'MIR, and then comparing the mRNA levels of MAP1B to levels in uninfected cells. *Id.* Messenger RNA levels were measured using quantitative reverse transcription polymerase chain reactions ("qRT-PCR") and expressed as a 50-Ct cycle threshold value. *See Id.* at item 5.

The experiments are based on the following logic: if HIV does not express the 3'MIR and these nucleic acids do not target MAP1B, then one of skill would predict that infecting cells with HIV would have no effect on MAP1B expression. On the other hand, if the HIV does express the 3'MIR and this nucleic acid inhibits expression of MAP1B, then one of skill would expect that infecting a cell with HIV would lead to a decrease in the level of MAP1B. The experiments described in the Chajut Declaration demonstrate that infecting c.Magi cells with HIV results in a significant 2.5-fold reduction in the level of MAP1B mRNA compared to uninfected cells ($p=0.007335$). *See Id.* at item 6. Accordingly, these results are consistent with those one of skill would predict for a virus that expresses the 3'MIR that targets MAP1B mRNA. In view of the foregoing, Applicant submits that nucleic acids related to the 3'MIR have a credible utility.

(4) Utility of the 5'MIR

Dr. Chajut also conducted experiments that confirmed that the 5'MIR is expressed in HIV-infected c.Magi cells. *See Id.* at item 7. Microarray experiments show that the level of the 5'MIR is higher in HIV-infected cells compared to the background levels demonstrated in uninfected cells. Applicant submits that the experiments described in the Chajut Declaration establish that the 5'MIR is expressed by HIV.

The experiments described above demonstrate that the claimed GAM2191 hairpin is processed into two miRNAs (the 5'MIR and 3'MIR). The experiments also show that the 3'MIR regulates expression of the target gene MAP1B. Accordingly, these experiments demonstrate that the bioinformatic prediction models disclosed in the specification accurately identify miRNAs and their targets, and in particular miRNAs of GAM2191 hairpin. Based on the success of the

bioinformatics prediction, one of skill would also reasonably expect that the 5'MIR interacts with the various target mRNA transcripts shown in Table 2, lines 151,383-151,482. In view of the foregoing, Applicant submits that specific, substantial and credible utility also exists for the claimed 5'MIR as set forth in SEQ ID NO: 5264.

(5) Utility of variants

On page 9 of the Office Action, the Examiner assets that neither the disclosure or literature provide any reason to believe that sequences less than 100% identical to the instant sequences will inhibit the target HIV gene. Applicant submits that the data presented in the Chajut Declaration and Table 2, line 151,383-151,482 shows that the interaction between the 3'MIR and its target gene MAP1B does not require 100% sequence complementarity. Furthermore, the 5'MIR/target gene interactions depicted in Table 2, lines 151,383-151,482 also show that less than 100% sequence complementarity is sufficient for binding. In view of the foregoing evidence of specific, substantial, and credible utility for the claimed nucleic acid and variants thereof, Applicant requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 101. Additionally, because the GAM2191 hairpin related nucleic acids are supported by a specific, substantial, and credible utility, Applicant respectfully requests that the Examiner reconsider and withdraw the claim rejections under 35 U.S.C. § 112, first paragraph.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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